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(19) (CA) **CANADIAN PATENT** (12)

(54) Active Compound Release Systems

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Active compound release systems

470 801

ABSTRACT

In a therapeutic system such as a plaster for administration of an active compound through the skin and comprising a covering layer which is essentially impermeable to the active compound, an active compound reservoir layer and a protective layer which can be pulled off and which is essentially impermeable to the active compound, the improvement wherein the reservoir layer contains about 1 - 30% of active compound in an elastomer mixture comprising a predominantly amorphous olefinic (co)polymer with a glass transition temperature of $\leq$ 20°C, mixed with from 0 up to about 50% by weight of a polyisobutylene, polybutadiene oil and/or paraffin oil, and a tackifying resin. Thereby the active compound can be released in regulated relatively large quantity over a prolonged period of time.

The invention relates to a system for the release of an active compound onto the skin over a prolonged period, in particular to antiphlogistic medicinal plasters.

U.S. Patent Specification 4,031,894 describes medicinal plasters which have a reservoir of a mixture of polyisobutenes with very different molecular weights, in particular molecular weights of 35,000 - 50,000 and 1,000,000 - 1,500,000, and mineral oils.

These plasters are suitable only for active compounds which are administered in very small doses. Scopolamine is mentioned in the U.S. patent specification.

DOS (German Published Specification) 3,007,368 describes plaster compositions which contain active compounds and, as the polymer component, thermoplastic elastomers of the A-B-A or $(A-B)_nX$ type, which largely contain vinylaromatics, preferably styrene, giving them thermoplastic processability.

Known active compound release systems, such as, for example, gels, ointments, known plasters and the like, allow only a limited absorption of active compound through the skin. The absorption depends on the base and the properties of the active compound.

An object of the present invention is to develop medicinal plasters with the aid of which regulated, relatively large therapeutically effective amounts of an active compound can be administered via the skin for a prolonged period. These plasters should be particularly suitable for the administration of antiphlogistics. They should be tolerated by the skin and with their aid it should be possible to administer high therapeutically effective doses of the active compound.

Surprisingly, it has now been found that corresponding plaster compositions with significantly increased rates of release of antiphlogistic active compounds are

obtained if particular rubber-like, predominantly amorphous, olefinic (co)polymers with glass transition temperatures of less than 20°C, if appropriate also in combination with suitable diene rubbers or styrene/diene rubbers, are used as the polymer component.

The present invention thus provides a therapeutic system for the administraiton of an active compound to the skin. The system includes an upper covering layer that is essentially impremeable to the active compound, an active compound reservoir layer and a protective layer which can be pulled off and is essentially impermeable to the active compound. The reservoir layer contains 1 to 30% of an antiphlogistic agent as the active compound in an elastomeric mixture. The elastomeric mixture comprises a rubber-like, predominantly amorphous, olefinic polymer or copolymer having a glass transition temperature of less than 20°C, an entraining agent and a tackifying resin. The predominantly amorphous olefinic polymer or copolymer is selected from the group consisting of (i) a homopolymer of cycloolefin, (ii) a copolymer of two different (C_2-C_{18})α-olefins or cycloolefins, and (iii) a copolymer of two different (C_2-C_{18})α-olefins or cycloolefins copolymerized with a diolefin, said diolefin containing copolymer having a molecular weight from 20,000 to 1 x 10^6, wherein the predominantly amorphous olefinic polymer or copolymer may up to 95% by weight of the total amount thereof be replaced by a diene rubber or a diene rubber copolymerized with an α-olefin.

The therapeutic system of the invention may in a practical form be called as a plaster. The active compound reservoir preferably contains 2-15 parts by weight of the antiphlogistic active compound, 30-60% by weight of the rubber-like polymer, 30-60% by weight of the entraining agent and 2-40% by weight of the tackifying resin, the last three components adding up to 100% by weight.

The polymers which are to be used according to the invention are products which are known in principle and which are commerically available from various companies.

Examples of the polymers to be used according to the invention are polyoctenamers (for example Vestenamer 8012® or Vestenamer A9® from Chem. Werke Hüls AG) and ethylene/propylene copolymers which contain small amounts of minor component incorporated either randomly or in blocks, preferably in blocks. Such products are described, for example, in Angew. Chem. 73, 196 (1961).

Examples of further polymers are copolymers of ethylene and/or propylene and other C_4-C_{18}- α-olefines, preferably of ethylene with C_4-C_{12}-α-olefines.

Examples of α-olefine copolymers copolymerised with dienes are products which are known as EPDM rubbers and which preferably consist of 20-90 parts by weight of ethylene, 10-80 parts by weight of propylene and 2-15 parts by weight (particularly preferably 4-10 parts by weight) of a non-conjugated diene. Of the large number of possible dienes, dicyclopentadiene,

D

ethylidenenorbornene and hexa-1,4-diene are particularly preferred diene components.

EPDM polymers which are particularly preferably to be employed in the context of the invention are those with molecular weights M_w of 20,000 to about M_w of 1 x 10^6, preferably M_w of up to 500,000. The polymers to be used according to the invention can be used by themselves or in mixtures of several polymers of the polymers described, and also in combination with amorphous polyisobutenes which have a molecular weight distribution M_w/M_n of 1.5 -3.5, preferably 2.0 - 3.0.

The diene rubbers which are suitable for combination with the abovementioned polymers are likewise products which are known to the expert and which can be prepared on the basis of 1,3-dienes, such as butadiene,

isoprene, piperylene and 2,3-dimethylbutadiene, preferably butadiene, in various ways which are known to the expert, it being possible to vary widely the nature of the double bonds in the polymer, depending on th choice of the metal catalyst (see, for example, Ullmanns Encyclopädie d. techn. Chemie (Ullmann's Encyclopaedia of industrial chemistry), 4th edition, volume 13, pages 602-611, Verlag Chemie, Weinheim/New York (1977).

Diene rubbers with more than 80 % of cis-1,4-linkages are preferably used. Natural rubber is also suitable in the context of the parameters mentioned.

Examples of vinyl-aromatics which are suitable for combination with the diene rubbers are styrene, α-methylstyrene, vinyltoluenes, p-ethylstyrene, dimethylstyrenes and 4-vinyldiphenyl, preferably styrene. The diene rubbers modified with vinyl-aromatics are also products which are known, for example as "styrene/butadiene rubber", and which can be prepared by known processes such that the vinyl-aromatic content is incorporated not only randomly but also partly or predominantly as a block structure in the diene rubber.

The amorphous (co)polymers from α-olefines or the EPDM rubbers by themselves are preferably used as the polymer components. In some particular cases, especially in order to prevent the separation of active compounds, for example by crystallisation, in the long term, a mixture with selected diene rubbers, preferably with up to 50 % by weight of the total amount of polymer, may be advantageous.

Entraining agents in the context of the present invention are understood as meaning oils, fatty acid esters, triglycerides, alcohols and/or fatty acids.

Oils in the context of the present invention are understood as meaning high-boiling aliphatic, araliphatic and/or aromatic hydrocarbons, preferably paraffin oil, Purcellin oil, perhydrosqualene and solutions of microcrystalline waxes in the oils, and mineral oils, preferably oils with a boiling range between 150°C and 400°C; and furthermore unsaturated hydrocarbons with at least 16 C atoms, such as, for example, oligomers of monoolefines, such as t traisobutyl ne, pentaisobutylene and

hexaisobutylene, or liquid polymers of diene(monoene)(co)-polymers. Examples of liquid polymers of conjugated dienes are those of butadiene, isoprene, penta-1,3-diene, 2,3-dimethylbutadiene, copolymers of various dienes and liquid copolymers of a conjugated diolefine and small amounts of monoolefines, such as, for example, but-1-ene, isobutene, hex-1-ene, oct-1-ene and styrene, with molecular weights of 400 to 6,000, preferably 800 to 3,000, iodine numbers of 200 to 500 and viscosities of 100 - 10,000 cP at 50°C

Liquid polybutadiene polymers which are at least 90 % 1,4-linked, in which the content of cis-double bonds is more than 60 % and which have molecular weights of 1,000 to 4,000 are particularly preferred.

Oils are also understood as meaning silicone oils of various viscosities, preferably with average molecular weights of 312 to 15,000, particularly preferably polydimethylsiloxanes.

Fatty acid esters are understood as meaning those which contain at least 12 C atoms, preferably 15 to 46 C atoms and particularly preferably 16 to 36 C atoms. By these there are understood, in particular: ethyl stearate, hexyl laurate, dipropylene glycol pelargonate, cetyl palmitate, isopropyl myristate, isopropyl palmitate, caprylic/capric acid esters of saturated fatty alcohols of C_{12}-C_{18} chain length, isopropyl stearate, oleyl oleate, decyl oleate, ethyl oleate and synthetic duck uropygial gland fat, in each case individually or as a mixture.

Triglycerides are understood as meaning pure or mixed esters of glycerol and fatty acids of C_8-C_{18} chain length, preferably caprylic and/or capric acid triglycerides.

Fatty acids are understood as meaning saturated or unsaturated fatty acids, preferably those with 12-24 C atoms, by themselves or as mixtures with one another,

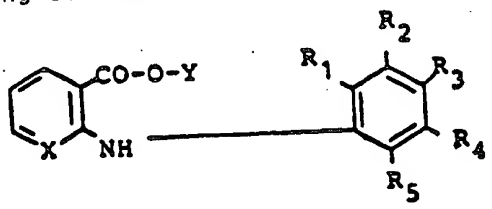
particularly preferably oleic acid.

Oils in the context of the invention are furthermore understood as meaning: sweet almond oil, avocado oil, sesame oil, castor oil, oliv oil, grape seed oil, clove oil, groundnut oil, maize oil, hazelnut oil, jojoba oil, carthama oil and wheatgerm oil, in each case by themselves or as a mixture.

Resins in the context of the present invention are understood as meaning rosin, dehydrogenated rosin, glycerol esters of dehydrogenated rosin, glycerol esters of rosin gum, hydrogenated rosin, glycerol esters of hydrogenated rosin, pentaerythritol esters of hydrogenated rosin, methyl esters of hydrogenated rosin, polymerised rosin, glycerol esters of polymerised rosin, terpene resins, coumarone/indene resins, hydrogenated petroleum resins, rosin modified by maleic anhydride and rosin derivatives, C_5-petroleum resins and half-esters of styrene/maleic acid copolymers, by themselves or as mixtures with one another. Polyterpene resins of alpha- or beta-pinene or modified glycerol esters of rosin are particularly preferred. Depending on the properties required in respect of tackiness and adhesion to the part onto which the resulting plaster is to be applied, these resins can be used either by themselves or in combination with one another.

Antiphlogistics in the context of the present invention are one or more antiphlogistics of the general formula I and/or II.

Antiphlogistics of the general formula I have the following structure:



I

wherein

R_1 - R_5 can be identical or different and denotes hydrogen, halogen, lower alkyl or substituted alkyl,

X denotes N or CH and

Y denotes hydrogen, metal ions, alkyl or substituted alkyl.

Halogen denotes fluorine, chlorine or bromine, preferably chlorine and/or bromine and particularly preferably chlorine. Lower alkyl is preferably alkyl with 1 - 6 C atoms, particularly preferably 1 - 4 C atoms, and substituted alkyl R_1 - R_5 preferably denotes trihalogenoalkyl, particularly preferably trifluoromethyl. Metal ions are understood as meaning the ions of alkali metals, alkaline earth metals or aluminium, preferably sodium. Substituted alkyl Y preferably denotes alkoxy, alkoxyalkyl, hydroxyalkyl, hydroxyalkoxyalkyl or trihalogenoalkyl, in which the number of C atoms is 1 to 6 and the alkyl chain can be straight or branched.

Antiphlogistics which are preferably used are those of the general formula I
in which

R_3 and R_4 denote hydrogen,

X denotes nitrogen or a CH group,

Y denotes hydrogen, C_1-C_4-alkyl or substituted C_1-C_4-alkyl, hydroxyalkyl or hydroxyalkoxyalkyl with 1 to 6 C atoms and

R_1, R_2 and R_5 denote hydrogen, chlorine, C_1-C_4-alkyl or trifluoromethyl.

Particularly preferred antiphlogistics of the general formula I are those
in which

X represents a CH group,

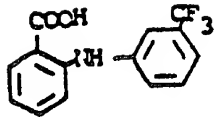
Y denotes hydrogen or hydroxyalkoxyalkyl with 1 to 6 C atoms and

R_1, R_2 and R_5 denote methyl, hydrogen, tri-

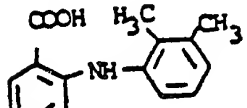
fluoromethyl or chlorine.

The following antiphlogistics are very particularly preferred.

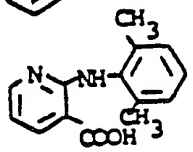
N-(α,α,α-Trifluoro-m-tolyl)-anthranilic acid = flufenamic acid



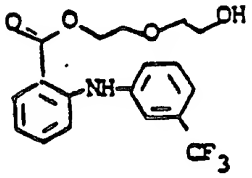
N-(2,3-Xylyl)-anthranilic acid



2-(2,6-Xylidino)-nicotinic acid



2-(2-Hydroxyethoxy)-ethyl N-(α,α,α-trifluoro-m-tolyl)-anthranilate = etofenamate



Antiphlogistics in the context of the present invention are furthermore antiphlogistics of the general formula II having the structure:

$$Ar-(-\overset{O}{\overset{\|}{C}}-)_p-(\overset{R}{\overset{|}{C}}H)_n-(CH_2)_m-COOH, \qquad II$$

in which

R denotes hydrogen, lower alkyl or substituted alkyl,

Ar denotes aryl, heteroaryl, substituted aryl or substituted heteroaryl,

(n + m) denotes an integer and has the value zero, 1 or 2, and

p denotes zero or 1,

with the conditi n that Ar does not denote aryl or hetero-aryl if n, m and p have the value of zero, and est rs or amides thereof.

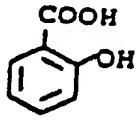
R preferably denotes lower alkyl radicals with 1 - 6 C atoms, preferably 1 - 4 C atoms, substituted alkyl, alkoxyalkyl or trihalogenoalkyl; aryl or heteroaryl, for example phenyl, naphthyl, thiophenyl, pyrrolyl, indenyl, indolyl, benzothiazinyl or phenothiazinyl.

Substituents for aryl or heteroaryl are alkyl, preferably straight-chain or branched alkyl with up to 6 C atoms, alkoxy, hydroxyalkyl, acyl, hydroxyl, acetoxy, benzoyl, substituted benzoyl, phenyl, substituted phenyl, phenoxy, halogen, phenylalkenyl and phenylalkyl.

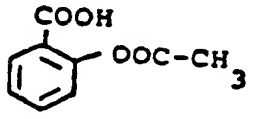
The esters are alkyl esters with 1 - 6 C atoms, preferably 1 - 4 C atoms in the alcohol component, particularly preferably methyl, ethyl, i- and n-propyl, substituted alkyl, for example β-hydroxyethyl, esters of glycolic acid. The amides can also contain lower alkyl or substituted alkyl radicals in the grouping $-CO-NH_2$ instead of one or both of the amide hydrogens.

The following antiphlogistics of the general formula II are particularly preferred:

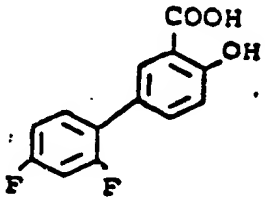
2-Hydroxybenzoic acid



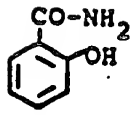
2-Acetoxybenzoic acid



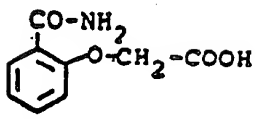
2',4'-Difluoro-4-hydroxy-3-biphenylcarboxylic acid



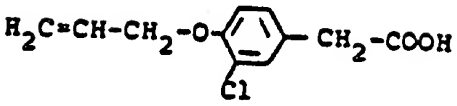
2-Hydroxybenzamide



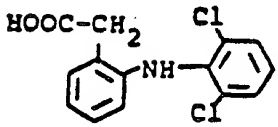
[2-(aminocarbonyl)phenoxy]-acetic acid



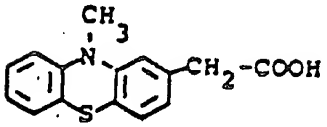
4-Allyloxy-3-chlorophenyl-acetic acid
= alclofenac



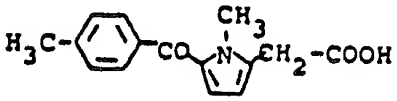
2-[(2,6-Dichlorophenyl)amino]-phenylacetic acid



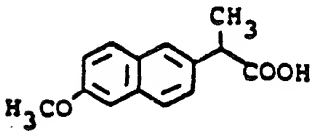
10-Methyl-phenothiazin-2-yl-acetic acid
= metiazinic acid



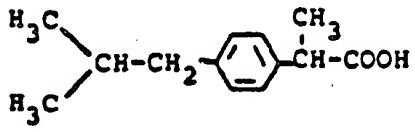
1-Methyl-5-(p-toluoyl)-pyrrol-2-yl-acetic acid



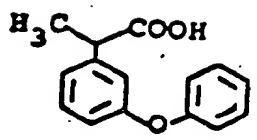
D-2-(6-Methoxy-2-naphthyl)-propionic acid
= naproxen



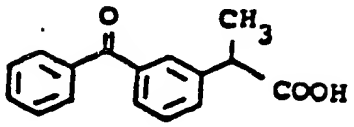
2-(p-Isobutylphenyl)-propionic acid



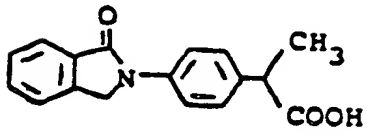
2-(3-Phenoxyphenyl)-
propionic acid



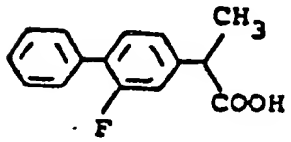
2-(m-Benzoylphenyl)-
propionic acid
= ketoprofen



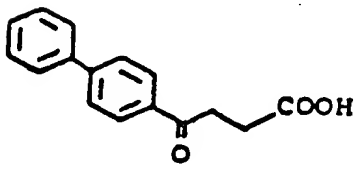
2-[4-(1-Oxo-2-isoindolinyl)-
phenyl]-propionic acid
= indoprofen



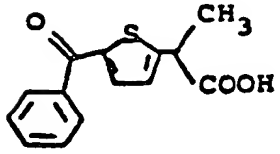
2-(2-Fluorobiphenyl-4-yl)-
propionic acid



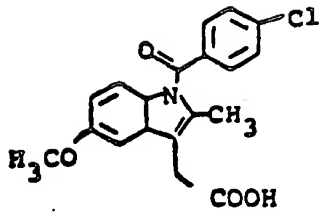
3-(4-Biphenylcarbonyl)-
propionic acid



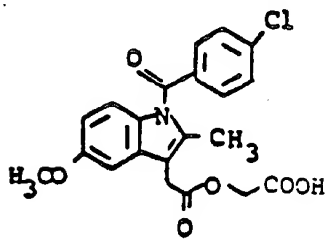
2-(5-Benzoyl-2-thienyl)-
propionic acid



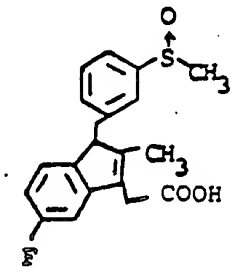
1-(p-Chlor benzoyl)-5-methoxy-2-methylindole-3-acetic acid
= indometacin



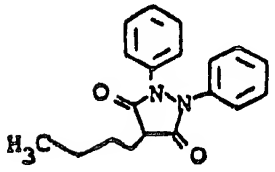
1-(p-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetoxyacetic acid
= acemetacin



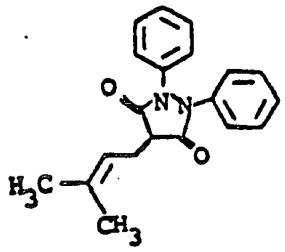
(Z)-5-Fluoro-2-methyl-1-[(4-methylsulfinyl)phenyl]-methylene)-1H-indene-3-acetic acid



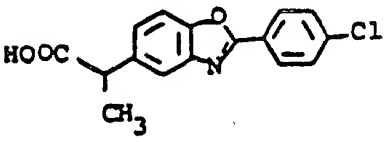
4-Butyl-1,2-diphenyl-3,5-pyrazolidine-dione
= phenylbutazone



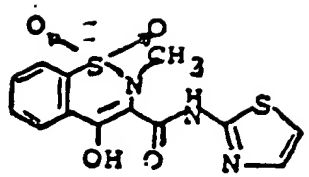
4-(3-Methyl-but-2-enyl)-1,2-diphenyl-pyrazolidine-3,5-dione
= feprazone



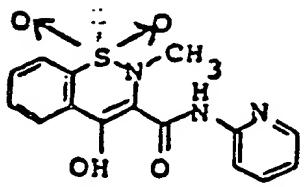
2-(4-Chlorophenyl)-2-methyl-5-benzoxazoleacetic acid
= benoxaprofen



N-(2-thiazolyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide



N-(2-pyridinyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide (keto/enole mixture)



and alkyl esters and substituted alkyl esters thereof.

Either one or more of the abovementioned antiphlogistics of the general formulae I and II can be incorporated into the plasters.

The antiphlogistics can be incorporated into the reservoir layer in an amount of 1-30 % by weight, preferably 2-20 % by weight. The % by weight given relates to the total reservoir.

Other active substances or cooling or fragrance-releasing substances, preferably methyl salicylate, glycol salicylate, salicylic acid, menthol, peppermint oil, camphor, thymol, Acrinol, scopola extract, chloropeniramine maleate, benzyl nicotinate, capsicum extract, nonylvanillylamide and capsaicin, can also additionally be added to these antiphlogistics.

If necessary, additives and fillers, for example antiageing agents, antioxidants and reinforcing fillers, can be added to the plasters according to the invention as long as the gel-like properties are not destroyed.

Known active compound release systems, such as, for example, gels, ointment bases and plasters, release about 0.5 - 5 mg of active compound in 4 hours. In contrast, the therapeutic system according to the invention

described above releases up to 18 mg of active compound in 4 hours, with a significantly greater bioavailability. The rate of release of the active compound from the systems according to the invention can be adjusted to almost any desired value by changing the polymer content, the entraining agent or the resin.

The reservoir containing the active compound and the plaster based thereon can be produced, for example, as follows: the plaster bases (polymer, resin and entraining agent) are introduced into a suitable dissolving vessel and are dissolved in benzine, with stirring. A clear to slightly turbid solution 1 results. The active compound component is also dissolved in a suitable solvent, and the solution is added to polymer solution 1.

The resulting solution 2 containing active compound is applied uniformly to siliconized paper and drawn to a film. The coated paper with the plaster base is dried in air for 24 hours and then kept in a circulating air drying cabinet at 40°C for 1 hour.

The rates of release of active compound are determined in an absorption model described in more detail in the experimental section with reference to the accompanying drawings in which:

Figure 1 schematically illustrates apparatus used to test for in vitro release of active compound from acceptor medium, and

Figure 2 is a sectional side elevation of a resorption cell.

Testing in vitro of the release of the plasters according to the invention

All the plasters were produced in the same manner, with 10% of active compound component, from polymer, entraining agent, resin and, if appropriate, solvent (benzine, hexane-or a hexane/toluene mixture). The particular proportions used are given in the recipe descriptions.

For this, all the components were dissolv d or suspend d. Acetone and/or ethanol were chiefly used as the solvents for the active compound.

These solutions or suspensions were processed to films 50 - 150 µm thick.

Experimental parameters:

- acceptor medium	:	mixture of water ethanol, PVP and sorbitan fatty acid ester
- volume of the acceptor medium	:	200 ml
- temperature of the acceptor medium	:	35 - 36°C
- pump capacity	:	16 ml/minute (apparatus constant)
- membrane	:	the film described in Example 3 of DE-OS (German Published Specification) 3,312,735 was used as the membrane
Absorption area	:	33.18 cm^2 (cell constant)

The acceptor medium was heated to the required temperature in a stock vessel and pumped around the absorption cells via tubes. Samples were withdrawn between the pump and the absorption cells.

Figure 1 shows a hose pump 1 for the acceptor medium 5 and a hose pump 2 for heating fluid which circulates through hose 4. A sample of acceptor medium is removable at valve/tap 3. The heating vessel 6 holds the heating fluid. There is a resorption cell 7 with a membrane.

Figure 2 illustrates the resorption cell 7 with an opaque cell material 1 and a membrane 2. The cell 7 has a viewing window 3 of glass with a corrugated surface.

Sampling was effected at specified intervals of time. In each

case 6 ml of sample were withdrawn and measured by spectrophotometry. The acceptor liquid was not replaced, since this would mean a dilution of the remainder.

Calculation of the results

A calibration curve was first recorded for the particular active compound component, with the aid of which the active compound concentration (mg or %) in the individual samples was determined from the extinction values measured for the individual samples. The extinctions were measured by UV spectroscopy.

To calculate the "relative absorption" (proportion of "absorbed" active compound of the total content of the plaster in %), it is necessary to know the amount of active compound employed. The content of active

compound of a defined plaster size (33,18 cm^2) is known from the production of the plaster;

The concentration of active compound in the sample was determined from the extinction values measured for the individual samples, with the aid of a calibration line or the factor determined therefrom.

$$M_i(t) = V_t \cdot C_i + M_F(t) \; [mg]$$

$$M_F(t) = \sum_{i=0}^{i=n-1} (V_D \cdot C_i) \; [mg]$$

$M_i(t)$: amount of drug released up to time t [mg]
V_t : volume of the acceptor at time t [ml]
C_i : active compound concentration in the sample in question [mg/ml]
$M_F(t)$: amount of active compound removed up to time t [mg]
V_D : sample volume [ml]
n : number of samples up to time t
t : duration of the experiment

Description of the preparation

The active compound release systems according to the invention were produced as follows: the mixture of polymer, resin and entraining agent were prekneaded in a Z-kneader at a temperature of 120 to 150°C. When the mass was a homogeneous melt, the active compound was homogeneously incorporated, while gassing with nitrogen. The

melt containing active compound was applied to the carrier film (kneader).

The active compound rel ase syst ms according to the invention were dissolved in a solvent mixture and the solution was applied to the carrier film and then dried (solution).

Example series A: standard (not according to the invention)

In this series of experiments, a styrene/isoprene/styrene TR block copolymer ("Cariflex* TR 1107 from Shell Chemical Company) was used as the polymer, thinly liquid paraffin was used as the entraining agent and a polyterpene resin from β-pinene was used as the tackifying resin.

The styrene/isoprene/styrene TR block copolymer plaster containing 10 % of active compound was used as the reference standard in all the further experiments.

The precise composition of the plaster base is given in Table 1. The plaster was produced as described above. The rates of release are described in Table 2.

Table 1 Composition of the standard formulation

Styrene/isoprene/styrene/TR block copolymer	36.0 g
Thinly liquid paraffin	45.0 g
Polyterpene resin from β-pinene	9.0 g
Etofenamate	10.0 g

Table 2 Release from the experimental standard series as a function of time

	Amount of etofenamate released in mg/hour						%	Amount of etofenamate weighed out in mg
	0.5	1	1.5	2	3	4		
Standard 10%	1.44	2.16	2.70	3.24	4.63	4.81	21.20	22.77

* trademark

Example series B

In this series of experiments, the composition of the polymers was varied. The precise description of the polymers is giv n in Table 3.

The plasters were produced as described above.

The amounts of all the polymers listed in Table 3 were varied in accordance with the following scheme, the paraffin oil and resin content remaining constant:

	A1	A2
Polymer	36.0 g	45.0 g
Thinly liquid paraffin oil	45.0 g	37.5 g
Polyterpene resin from β-pinene	9.0 g	7.5 g
Etofenamate	10.0 g	10.0 g

The rates of release are described in Table 4.

Table 3

Example series B: description of the polymers used. The two first numbers designate the polymer, the designation of the formulation being given instead of x (see above, A1 or A2).

No. 01 x polyoctenamer; cis/trans ratio about 20:80, viscosity number I at 25°C: 120 ml/g glass transition temperature T_G - 65°C

02 x EPDM - terpolymer with about 45 % by weight of propylene, ethylidenenorbornene as the diene component, iodine number about 13, Mooney plasticity (1+4) minutes running time, 100°C : 45

03 x as 02, but with about 30 % by weight of propylene, iodine number about 13, Mooney plasticity (1+4) minutes running time, 100°C : 35

04 x as 03, grafted with 9 % of styrene/butadiene, iodine number about 15

05 x EPDM - terpolymer (3 % of ethylidenenorbornene) with about 60 parts by weight of propylene, iodine number about 7, Mooney plasticity 65

06 x as 05, with 6 % of ethylidenenorbornene, iodine number about 12, Mooney plasticity 55

07 x as 05 , with 6 % of dicyclopentadiene, iodine number about 12, Mooney plasticity 40

Table 4

Example series B: release as a function of the time

No.	Etofenamate released (mg) in hours 0.5	1	1.5	2	3	4	%	Amount of etofenamate weighed out in mg
Standard	1,44	2.16	2,70	3.24	4.63	1.81	21,20	22.77
01 A1	3.57	5.05	6.20	7,55	9,48	10.82	54,15	19,99
01 A2	2.45	5,71	7.53	8.83	11,92	14,00	45,73	30,62
02 A1	4,39	5.82	7.45	9.03	11.57	12,63	56,12	22.50
02 A2	4.79	6.48	8,44	10,02	12,85	14,88	53.58	27,78
03 A1	3.67	5.45	7.12	8.31	10.28	11,67	43.70	26.71
03 A2	3,83	6,05	8.16	10.96	12,65	12.65	47.02	26,90
04, A1	2,86	4,19	5.29	6.64	9,63	9,78	50,14	19.51
04 A2	2.65	3.64	4.70	5,71	7.06	8,71	49,13	17.73
05 A1	3.82	6,45	9,23	10,99	13.72	15.67	67,91	23.09
05 A2	3.72	6,34	8,41	10.59	13,46	15,54	47,86	32.47
06 A1	4,90	6.68	8,35	9,89	12.18	13.61	55,40	24.56
06 A2	3.47	5.69	8.33	9,71	12.19	14,10	47,01	29.99
07 A1	5,71	7.54	9,41	11,17	13,60	14,94	54,28	27.53
07 A2	3,93	6,65	8,52	10,65	13.35	15,21	52,70	28.86

Example series C: Variation of the liquid components

The liquid component of the formulations chosen from Example series B was changed in composition according to the following scheme, the remainder of the recipe being retained.

	B1	B2
Polymer	as in Example series B	
Liquid component	Polybutadiene oil of molecular weight 1,500	Polybutadiene oil of molecular weight 1,500 + thinly mobile paraffin oil 1:1
Etofenamate	10 %	10 %

The precise composition of the plaster bases are given in Table 5 and the rates of release are given in Table 6.

Table 5

Example series C: Composition of the formulations

No.	Polymer	Liquid component: liquid polybutadiene oil	Liquid component: thinly mobile paraffin oil	Resin	Etofenamate
02A2	45 %	-	37,5 %	7.5 %	10 %
02B1	45 %	37.5 %	-	7,5 %	10 %
02B2	45 %	18.75 %	18.75 %	7.5 %	10 %
07A1	36 %	-	45 %	9 %	10 %
07B1	36 %	45 %	-	9 %	10 %
07B2	36 %	22.5 %	22.5 %	9 %	10 %
07A2	45 %	-	37.5 %	7.5 %	10 %
07B1	45 %	37.5 %	-	7.5 %	10 %
07B2	45 %	18.75 %	18,75 %	7.5 %	10 %

Table 6

Example series C: Release as a function of time

No.	Etofenamate released (mg) in hours 0.5	1	1.5	2	3	4	%	Amount of etofenamate weighed out in mg
Standard	1.44	2.16	2.70	3.24	4.63	4.81	21.20	22.77
02A2	4.79	6.48	8.44	10.02	12.85	14.88	53.58	27.78
02B1	3.11	4,69	6,18	7.57	10,04	11.95	42.52	28.10
02B2	3.52	5,15	7,16	8,60	11.12	13.24	42,14	31.42
07A1	5.71	7,54	9.41	11.17	13.60	14.94	54.28	27.53
07B1	2.04	3.68	5,54	6.80	9,89	12,28	35.00	35,08
07B2	1,99	3.47	5.24	6,59	9.37	11.46	40.97	27,96
07A2	3,93	6,65	8.52	10,65	13.35	15.21	52,70	28.86
07B1	2.55	4,73	6,60	8,31	11.46	13.62	44.23	30.80
07B2	2,55	4,58	6,64	8,22	11,41	13.88	42.57	32.59

Example series D: Variation of the resin content

Table 7

Recipes with a changed resin content

No.	Polymer	Paraffin	Resin	Etofenamate
02A2	45 %	37.5 %	7.5 %	10 %
02C1	43.2 %	36 %	10.8 %	10 %
02C2	41.5 %	34.6 %	13.9 %	10 %

Table 8

Release with the changed resin content

N.	Etofenamate released (mg) in hours 0,5	1	1,5	2	3	4	%	Amount of etofenamate weighed out in mg
Standard	1.44	2.16	2,70	3,24	4,63	4,81	21,20	22,77
02A2	4.79	6,48	8,44	10,02	12,85	14.88	53,58	27,78
02C1	3,42	5.74	8,04	9,57	11.73	13,42	51,59	26,01
02C2	2.19	3,87	5,31	6,43	8,54	10,05	32.68	30.76

Example 1 (solution)

Polyoctenamer; cis/trans ratio about 20:80	45.0 g
Thinly mobile paraffin	37.5 g
Polyterpene resin from β-pinene	7.5 g
Etofenamate	10.0 g

Release: 14.0 mg (45.73%) after 4 hours

Example 2 (solution)

EPDM terpolymer with about 45 % by weight of propylene, ethylidene-norbornene as the diene component, Mooney viscosity (1+4) minutes running time 100°C : 45	45.0 g
Thinly mobile paraffin	37.5 g
Polyterpene resin from β-pinene	7.5 g
Etofenamate	10.0 g

Release: 14.88 (53.58 %) after 4 hours

Example 3 (solution)

EPDM terpolymer with about 30 % by weight of propylene, Mooney viscosity (1+4) minutes running time 100°C: 35	36.0 g
Thinly mobile paraffin	45.0 g
Polyterpene resin from β-pinene	9.0 g
Etofenamate.	10.0 g

Release: 11.67 mg (43.7 %) after 4 hours

Example 4 (solution)

EPDM terpolymer with about 30 % by weight of propylene, grafted with 9 % of styrene/butadiene	36.0 g
Thinly liquid paraffin	45.0 g
Polyterpene resin from β-pinene	9.0 g
Etofenamate	10.0 g

Release: 9.78 mg (50.14 %) after 4 hours

Example 5 (solution)

EPDM terpolymer (3 % of ethylidene-norbornene) with about 60 parts by weight of propylene, Mooney viscosity (1+4) minutes running time 100°C:65	36.0 g
Thinly liquid paraffin	45.0 g
Polyterpene resin from β-pinene	9.0 g
Etofenamate	10.0 g

Release: 15.67 mg (67.91 %) after 4 hours

Example 6 (solution)

EPDM terpolymer (6 % of ethylidene-norbornene), Mooney viscosity (1+4) minutes running time 100°C : 55	36.0 g
Thinly liquid paraffin	45.0 g
Polyterpene resin from β-pinene	9.0 g
Etofenamate	10.0 g

Release: 13.61 mg (55.4 %) after 4 hours

Example 7 (solution)

EPDM terpolymer with 6 % of dicyclopentadiene, Mooney viscosity (1+4) minutes running time 100°C : 40	36.0 g
Thinly mobile paraffin	45.0 g
Polyterpene resin from β-pinene	9.0 g
Etofenamate	10.0 g

Release: 14.94 mg (54.28 %) after 4 hours

Example 8 (solution)

Polyoctenamer; cis/trans ratio about 20:80	36.0 g

Thinly liquid paraffin	22.5 g
Decyl oleate	22.5 g
Modifi d glycerol ester of rosin	9.0 g
Acemetacin	10.0 g

Release: 12.72 mg (52.71 %) after 4 hours

Example 9 (solution)

EPDM terpolymer with 5 % of dicyclopentadiene, Mooney viscosity (1+4) minutes running time 100°C : 40	36.0 g
Decyl oleate	22.5 g
Thinly mobile paraffin	22.5 g
Modified glycerol ester of rosin	9.0 g
Ketoprofen	10.0 g

Release: 10.21 mg (47.3 %) after 4 hours

Example 10 (solution)

EPDM terpolymer with 6 % of dicyclopentadiene, Mooney viscosity (1+4) minutes running tim 100°C : 40	36.0 g
Isopropyl myristate	22.5 g
Thinly liquid paraffin	22.5 g
Polyterpene resin from α-pinene	9.0 g
Acemetacin	10.0 g

Release: 10.21 mg (44.5 %) after 4 hours

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

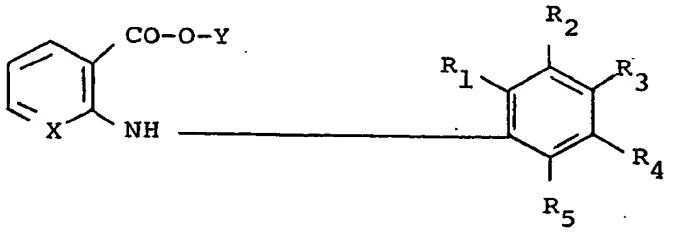
1. A therapeutic system including an active compound, an upper covering layer that is essentially impermeable to the active compound, an active compound reservoir layer and a protective layer that can be pulled off and that is essentially impermeable to the active compound, wherein the reservoir layer contains as the active compound 1 to 30% of an antiphlogistic agent in an elastomeric mixture, the elastomic mixture comprising (a) a predominantly amorphous olefinic polymer or copolymer having a glass transition temperature of less than 20°C selected from the group consisting of (i) a homopolymer of cycloolefin, (ii) a copolymer of two different (C_2-C_{18}) α-olefins or cycloolefins, and (iii) a copolymer of two different (C_2-C_{18}) α-olefins or cycloolefins copolymerized with a diolefin, said diolefin containing copolymer having a molecular weight from 20,000 to 1 X 10^6, wherein the predominantly amorphous olefinic polymer or copolymer may up to 95% by weight of the total amount thereof be replaced by a diene rubber or a diene rubber copolymerized with an α-olefin, (b) an entraining agent and (c) a tackifying resin.

2. A therapeutic system according to claim 1, which is a plaster for administration of the active compound through skin.

3. A therapeutic system according to claim 2, wherein the reservoir layer contains 30 to 60% by weight of the copolymer, 30 to 60% by weight of the entraining agent and 2 to 40% by weight of the tackifying agent besides the active compound, the percentages being based on the total amount of the three components.

4. A therapeutic system according to claim 3, wherein the entraining agent is polyisobutylene oil, polybutadiene oil, paraffin oil or a mixture thereof; the tackifying agent is rosin, dehydrogenated rosin, glycerol ester of dehydrogenated rosin, glycerol ester of rosin gum, hydrogenated rosin, glycerol ester of hydrogenated rosin, pentaerythritol ester of hydrogenated rosin, methyl ester of hydrogenated rosin, polymerized rosin, glycerol ester of polymerized rosin, terpene resin, coumarone resin, indene resin, hydrogenated petroleum resin, rosin modified by maleic anhydride, C_5-petroleum resin or half-ester of styrene/maleic acid copolymer.

5. A therapeutic system according to claim 4, wherein the active compound is one or more of the formula:



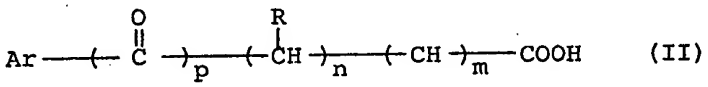
(I)

(wherein R_1 through R_5 can be identical or different and denote hydrogen, halogen, C_{1-6} alkyl or trihalogeno-C_{1-6} alkyl,

X denotes N or CH, and

Y denotes hydrogen, a alkali metal or alkaline earth metal or aluminium ion, C_{1-6} alkyl, C_{1-6} alkoxy-C_{1-6} alkyl, hydroxy-C_{1-6} alkyl, hydroxy-C_{1-6} alkoxy-C_{1-6} alkyl or trihalogeno-C_{1-6} alkyl), and

of the formula:



(II)

(wherein R denotes hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy-C_{1-6} alkyl or trihalogeno-C_{1-6} alkyl,

Ar denotes aryl selected from the group consisting of phenyl, naphthyl and indene or Ar denotes heteroaryl selected from the group consisting of thiophenyl, pyrrolyl, indolyl, benzothiazinyl and phenothiazinyl, in which each of the aryl and the heteroaryl may be substituted by C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy-C_{1-6} alkoxy, C_{1-6} acyl, hydroxy, acetoxy, benzoyl, phenyl, phenoxy, halogen, phenyl-C_{2-6} alkenyl or phenyl-C_{1-6} alkyl,

n and m are each an integer and the total of n + m is 0, 1 or 2, and

p is 0 or 1,

with the proviso that Ar cannot be the aryl or heteroaryl when n, m and p are 0)

or an ester or amide thereof.

6. A therapeutic system according to claim 5, which contains an active compound of the formula (I) in which:

R_3 and R_4 each denote hydrogen,

X denotes N or CH,

Y denotes hydrogen, C_{1-4} alkyl, hydroxy-C_{1-6} alkyl, trihalogenomethyl or hydroxy-C_{1-6} alkoxy-C_{1-6} alkyl, and

R_1, R_2 and R_5 each denote hydrogen, chlorine, C_{1-4} alkyl or trifluoromethyl.

7. A therapeutic system according to claim 5, which contains an active compound of the formula (I) in which:

X denotes CH,

Y denotes H or hydroxy-C_{1-6} alkyl, and

R_1, R_2 and R_5 each denote H, methyl, trifluoromethyl or chlorine.

8. A therapeutic system according to claim 6, which contains, as an active compound,

N-(α,α,α-trifluoro-m-tolyl)anthranilic acid (=flufenamic acid),

N-(2,3-xylyl)anthranilic acid, 2-(2,6-xylidino)nicotinic acid or

2-(2-hydroxyethoxy)ethyl N-(α,α,α-trifluoro-m-tolyl)anthranilate (=etofenamate).

9. A therapeutic system according to claim 5, which contains as an active compound of the formula (II),

2-hydroxybenzoic acid, 2-acetoxybenzoic acid,

2',4'-difluoro-4-hydroxy-3-biphenylcarboxylic acid,

2-hydroxybenzamide,

[2-(aminocarbonyl)phenoxy]acetic acid,

4-allyloxy-3-chlorophenylacetic acid (=alclofenac),

2-[(2,6-dichlorophenyl)amino]phenylacetic acid,

10-methylphenothiazin-2-acetic acid (=metiazinic acid),

1-methyl-5-(p-toluoyl)pyrrol-2-ylacetic acid,

D-2-(6-methoxy-2-naphthyl)propionic acid (=naproxen),

2-(p-isobutylphenyl)propionic acid,

2-(3-phenoxyphenyl)propionic acid,

2-(m-benzoylphenyl)propionic acid (=ketoprofen),

2-[4-(1-oxo-2-isoindolinyl)phenyl]propionic acid (=indoprofen),

2-(2-fluorobiphenyl-4-yl)propionic acid,

3-(4-biphenylcarbonyl)propionic acid,

2-(5-benzoyl-2-thienyl)propionic acid,

1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid (=indometacin),

1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetoxyacetic acid (=acemetacin),

(Z)-5-fluoro-2-methyl-1-[(4-methylsulfinyl)phenyl]methylene-1H-indene-3-acetic acid,

4-butyl-1,2-diphenyl-3,5-pyrazolidinedione (=phenylbutazone),

4-(3-methylbut-2-enyl)1,2-diphenylpyrazolidine-3,5-dione (=feprazone),

2-(4-chlorophenyl)-2-methyl-5-benzoxazoleacetic acid (=benoxaprofen),

N-(2-thiazolyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide, or

N-(2-pyridinyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide (keto/enol mixture),

or C_{1-6} alkyl ester thereof.

10. A therapeutic system according to claim 5, which contains as the active compound at least one member selected from the group consisting of etofenamate and ketoprofen.

11. A therapeutic system according to claim 1, 2 or 3, wherein the olefinic copolymer is an ethylene/propylene copolymer.

12. A therapeutic system according to claim 4, 5 or 6, wherein the olefinic copolymer is an ethylene/propylene copolymer.

13. A therapeutic system according to claim 1, 2 or 3, wherein the olefinic copolymer is a copolymer of (i) ethylene or propylene and (ii) a (C_4-C_8)α-olefin.

14. A therapeutic system according to claim 4, 5 or 6, wherein the olefinic copolymer is a copolymer of (i) ethylene or propylene and (ii) a (C_4-C_8)α-olefin.

15. A therapeutic system according to claim 1, 2 or 3, wherein the olefinic copolymer is an EPDM terpolymer consisting of 20 to 90 parts by weight of ethylene, 10 to 80 parts by weight of propylene and 2 to 15 parts by weight of a non-conjugated diene, each based on 100 parts of the total amount of the EPDM terpolymer.

16. A therapeutic system according to claim 4, 5 or 6, wherein the olefinic copolymer is an EPDM terpolymer consisting of 20 to 90 parts by weight of ethylene, 10 to 80 parts by weight of propylene and 2 to 15 parts by weight of a non-conjugated diene, each based on

100 parts of the total amount of the EPDM terpolymer.

17. A therapeutic system according to claim 7, 8 or 9, wherein the olefinic copolymer is an EPDM terpolymer consisting of 20 to 90 parts by weight of ethylene, 10 to 80 parts by weight of propylene and 2 to 15 parts by weight of a non-conjugated diene, each based on 100 parts of the total amount of the EPDM terpolymer.

18. A therapeutic system according to claim 1, 2 or 3, wherein the olefinic copolymer is an EPDM terpolymer consisting of 20 to 90 parts by weight of ethylene, 10 to 80 parts by weight of propylene and 2 to 15 parts by weight of a non-conjugated diene selected from the group consisting of dicyclopentadiene, ethylidenenorbornene and hexa-1,4-diene, the EPDM rubber having a weight average molecular weight (Mw) of 20,000 to 1 X 10^6, the parts by weight being based on 100 parts of the total amount of the EPDM terpolymer.

19. A therapeutic system according to claim 4, 5 or 6, wherein the olefinic copolymer is an EPDM terpolymer consisting of 20 to 90 parts by weight of ethylene, 10 to 80 parts by weight of propylene and 2 to 15 parts by weight of a non-conjugated diene selected from the group consisting of dicyclopentadiene, ethylidenenorbornene and hexa-1,4-diene, the EPDM rubber having a weight average molecular weight (Mw) of 20,000 to 1 X 10^6, the parts by weight being based on 100 parts of the total amount of the EPDM terpolymer.

20. A therapeutic system according to claim 7, 8 or 9, wherein the olefinic copolymer is an EPDM terpolymer consisting of 20 to 90 parts by weight of ethylene, 10 to 80 parts by weight of propylene

and 2 to 15 parts by weight of a non-conjugated diene selected from the group consisting of dicyclopentadiene, ethylidenenorbornene and hexa-1,4-diene, the EPDM rubber having a weight average molecular weight (Mw) of 20,000 to 1 X 10^6, the parts by weight being based on 100 parts of the total amount of the EPDM terpolymer.

21. A therapeutic system according to claim 1, 2 or 3, wherein the olefinic copolymer is:

(a) an ethylene/propylene copolymer,

(b) a copolymer of (i) ethylene or propylene and (ii) a (C_4-C_{18})α-olefin, or

(c) an EPDM terpolymer consisting of 20 to 90 parts by weight of ethylene, 10 to 80 parts by weight of propylene and 2 to 15 parts by weight of a non-conjugated diene, each based on 100 parts of the total amount of the EPDM terpolymer; and

up to 50% by weight of the olefinic copolymer may be replaced by a diene rubber which is based on butadiene, isoprene, piperylene, or 2,3-dimethylbutadiene and may be copolymerized with a vinyl-aromatic selected from the group consisting of styrene, α-methylstyrene, vinyltoluene, p-ethylstyrene, dimethylstyrene and 4-vinyldiphenyl.

22. A therapeutic system according to claim 4, 5 or 6, wherein the olefinic copolymer is:

(a) an ethylene/propylene copolymer,

(b) a copolymer of (i) ethylene or propylene and (ii) a (C_4-C_{18})α-olefin, or

(c) an EPDM terpolymer consisting of 20 to 90 parts by weight of ethylene, 10 to 80 parts by weight of propylene and 2 to

15 parts by weight of a non-conjugated diene, each based on 100 parts of the total amount of the EPDM terpolymer; and

up to 50% by weight of the olefinic copolymer may be replaced by a diene rubber which is based on butadiene, isoprene, piperylene or 2,3-dimethylbutadiene and may be copolymerized with a vinyl-aromatic selected from the group consisting of styrene, α-methylstyrene, vinyltoluene, p-ethylstyrene, dimethylstyrene and 4-vinyldiphenyl.

23. A therapeutic system according to claim 1, 2 or 3, wherein the olefinic polymer is polyoctenamer.

24. A therapeutic system according to claim 4, 5 or 6, wherein the olefinic polymer is polyoctenamer.

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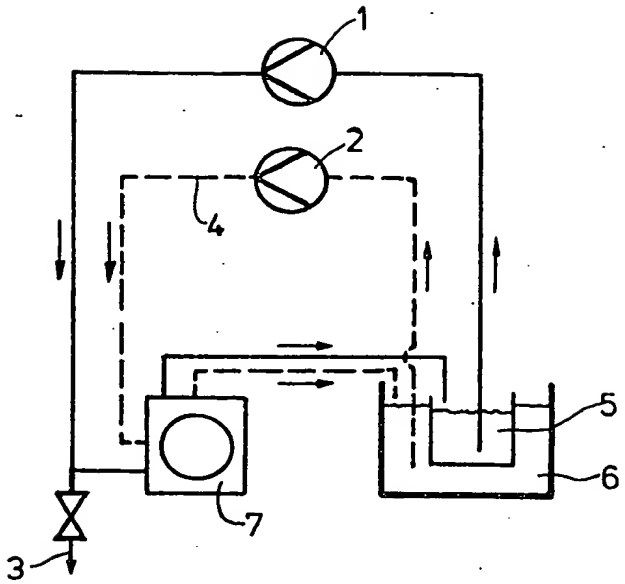

FIG. 1

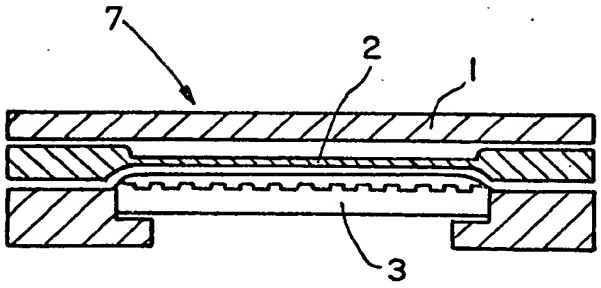

FIG. 2

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